REMARKS

This Amendment is in response to Examiner's Office Action mailed September 21, 2005 and Applicants' telephone interview with Examiners Parithosh K. Tungaturthi, Ph.D. and Larry R. Helms, Ph.D. on February 1, 2006. Claims 1-25 are canceled with prejudice. New claims 26-31 are added. Claims 26-31 are now pending.

Support for independent claim 26 appears in the specification, for example, in Figures 1A and 1C and their legend at page 2, lines 14-17. More specifically, support for the claim language "peptide linker 1 and peptide linker 3 are a peptide bond or have about 1 to about 10 amino acids" appears in the specification, for example, at page 6, lines 4-8; for the claim language "peptide linker 2 has 3 to about 10 amino acids" at page 6, lines 14-15. Support for the claim language "the antibody is bispecific for human CD3 and CD19 in dependent claim 29 appears in the specification, for example, at page 8, lines 4-8. Support for claim 30 appears in the specification, for example, in Figure 1A and its legend at page 2, lines 14-17, and in the section of EXAMPLES on pp. 8-13.

Reconsideration is respectfully requested in view of the following remarks.

I. Interview with Examiners

Applicants express appreciation to Examiner Tungaturthi and Examiner Helms for conducting a telephone interview with Applicants on February 1, 2006. During the interview Applicants discussed the issues raised by the Examiner in the Office Action mailed September 21, 2005, details of which are described in the following sections.

I. Claim Rejections – 35 USC § 112, First Paragraph

The Examiner has rejected claims 1-11, 20 and 21 under 35 U.S. C. 112, first paragraph, because the specification, while being enabling for a multivalent F_v antibody construct having at least four variable domains wherein two variable regions are light chain variable regions and two are heavy chain variable regions, does not reasonably provide enablement for a multivalent F_v antibody construct having any other combination of the number of heavy and/or light chain variable regions.

Applicants' cancellation of claims 1-25 renders the rejection moot. New independent claim 26 specifies a bispecific tetravalent homodimeric F_v antibody. As depicted in Figure 1C, the F_v antibody is a homodimer formed by a bispecific bivalent single-chain F_v antibody having at least four variable domains, V_H-A, V_L-A, V_H-B, and V_L-B. As acknowledged by the Examiner, these types of multivalent F_v antibody constructs are enabled. Withdrawal of the rejection is therefore respectfully requested.

II. Claim Rejections – 35 USC § 103(a)

The Examiner has rejected claims 1-11 and 20-21 under 35 U.S. C. 103(a) as being unpatentable over Mezes et al. (U.S. Pat. No. 5,892,020) in view of Hollinger et al. (U.S. Pat. No. 5,837,242) and Pastan et al. (U.S. Pat. No. 5,635,599) and Whitlow et al. (U.S. Pat. No. 5,856,456) and Coloma and Morrison (Nature Biotechnology 1997 Vol. 15:5-163; IDS – 08/21/05).

New independent claim 26 specifies a bispecific tetravalent homodimeric F_v antibody. As depicted in Figure 1C, the F_v antibody is a homodimer formed by a bispecific bivalent single-chain F_v antibody having at least four variable domains, V_H-A, V_L-A , V_H-B, and V_L-B. In addition, peptide linker 1 and peptide linker 3 are a peptide bond or have about 1 to about 10 amino acids and peptide linker 2 has about 3 to about 10 amino acids, No of the references cited, alone or in combination, teaches or suggests the claimed antibodies.

Specifically, the bispecific bivalent single-chain F_v antibody shown in Figure 1A forms a bispecific, **tetravalent, homodimer** (*see* Fig. 1C). The bispecific single-chain F_v antibody according to the invention comprises four covalently linked variable (V_H and V_L) domains of two different specificities connected by three linkers selected such that the pairing of the adjacent domains thereto is prevented; i.e. having up to about 10 amino acids. The formation of the homodimeric antibody is determined by the association of complementary V_H and V_L domains located on **different** polypeptide chains.

To establish a prima facie case of obviousness, the Examiner bears the burden of proving 1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; 2) the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention; and 3) one of ordinary skill in the art at the time the invention

was made would have reasonable expectation of success of the claimed invention. *In re Vaeck*, 947 F. 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re O'Farrell*, 853 F. 2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); and *In re Dow Chem.*, 837 F. 2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). In determining the scope and content of the prior art, references must be considered in their entirety, as a whole, including portions that would lead away from the claimed invention. *In re Panduit*, 810 F.2d 1561, 1 U.S.P.Q. 2d 1593 (Fed. Cir. 1987). Hindsight reconstruction using the disclosure and claims in prosecution as a guide to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention is not permitted. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988).

As discussed during the interview and in detail below, the claimed bispecific F_v antibody construct is completely different from the bispecific F_v antibody constructs of Mezes et al. and Holliger et al.

Mezes et al. refer to so-called $(scF_v)_2$ antibodies; i.e. two (or more) scF_v modules composed of two adjacent VH and VL domains of the same specificity. However, Mezes et al. do not teach or suggest tetravalent antibodies (i.e. having four antigen binding sites) or homodimers of polypeptide chains having four variable domains. Mezes et al. teach only to link two or more functional scF_v's of two adjacent complementary variable V_H and V_L domains which are linked such that they can pair to an antigen binding site with each other (see col.2, l. 33-36 and col. 2, l. 44-64). Mezes et al. do not suggest modifying the taught antibodies to switch to another antibody format. In particular, Mezes et al. do not suggest using a linker which prevents the pairing of adjacent variable domains.

Holliger et al. refer to so-called diabodies, i.e. **non-covalently** associated single-chains of **two different** fusion products each consisting of a V_H domain of one specificity connected to a V_L domain of the other specificity. Thus, Holliger et al. teach bispecific antibodies formed by **heterodimerization** of **two different gene products** which must be expressed in the same cell in similar amounts. In particular, Holliger et al. do not disclose or suggest switching to another antibody format to make a tetravalent bispecific antibody from the same polypeptide chain as claimed in the present application.

Hence, neither Mezes et al nor Holliger et al. suggest an F_v antibody which is bispecific and a homodime as specified in claim 26.

Further, the cited references does not contain any motivation for a skilled person to modify the constructs taught by Mezes et al. to obtain the antibodies according to the present invention because a skilled person would not have been motivated to modify the antibody construct of Mezes et al. with the short linker of Holliger et al. Holliger et al. teach that the short linker prevents the pairing of the connected two domains, while Mezes et al. require that the linker allows the association of its adjacent domains to form an antigen binding site.

Specifically, Mezes et al. disclose that the linker is generally about 10 to about 50 amino acids (col. 5, l. 36). However, Mezes et al. do not disclose or suggest that a linker of about 10 amino acids prevent pairing of its adjacent domains on the same polypeptide, because the teaching of Mezes et al. particularly requires that the linker for joining the variable domains allows its adjacent domains to fold **intramolecularly** into an antigen binding site (see col.2, l. 33-36; col. 2, l. 44-64 and col. 5, l. 1-13)

Thus, following the teaching of Mezes et al the replacement of the linkers of the construct of Mezes et al. by the short linker of Holliger et al. would result in the formation of non-functional scF_v molecules having domains which cannot pair with one another. Hence, there is no suggestion or motivation to modify the linkers of the construct of Mezes et al. with the short linker of Holliger et al.

As discussed during the interview, in fact, Holliger et al. teach away from Mezes et al., because Mezes et al. require that "*suitable linkers for joining the V_H and V_L domains are those which allow the V_H and V_L domains* [of a scF_v] *to fold into a single polypeptide chain*" (col. 5, l. 1-3) and that "*suitable linkers for linking the scF_vs are those which allow the linking of two or more scF_vs such that the V_H and V_L domains of <u>each</u>* [of the linked] *immunoglobulin fragment...maintains the binding specificity of the whole antibody...*" (col. 5, l. 7-13, emphasis and brackets added). Therefore, according to Mezes et al. and different from Holliger et al. the linkers for joining the V_H and V_L domains have to be long and flexible enough to allow the adjacent V_H and V_L domains of a scF_v to pair.

Pursuant to MPEP 2143.01V, if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

To modify the linkers of the construct of Mezes et al. with the short linker of Holliger et al. would render the antibody of Mezes et al. inoperable. Mezes requires long and flexible linkers for joining the V_H and V_L domains such that V_H and V_L domains [of a scF_v] to fold into a single polypeptide chain intramolecularly. A substitution with the short linker of Holliger et al. would prevent the pairing of the connected V_H and V_L domains.

Moreover, the remaining references also do not overcome the deficiencies of Mezes et al. and Holliger et al. to render the invention prima facie obvious. Pastan et al. teach altered ligands fused to an antibody (see, e.g. col. 14, l. 65 to col. 15, l. 52). Pastan et al. do not even disclose to fuse two antibodies or variable domains of antibodies with one another, let alone teach or suggest connecting linkers for connecting 4 variable domains with specified lengths in claims 26 and 30. Whitlow et al. discloses linkers having from about 2 to about 50 amino acids which will be applicable to <u>any</u> multi-chain protein (col. 9, l. 13). However, the length will depend upon the nature of the polypeptides to be linked (col. 9, l. 33-37 and col. 12, l. 8-10) and linkers used to construct scF_v polypeptides have between 10 and 30 amino acids; the linkers are designed to be long and flexible (col. 9, l. 54-56) ("*The requirements for a sFv is that the linker be longer than 12 amino acids.*" (col. 12, l. 10-11)). Thus, Whitlow et al. do not teach or suggest to use peptide bonds or linkers of 1 to 10 amino acids for sF_v. In fact, Whitlow et al. teaches away from the present invention as they disclose that [t]*he requirements for a sFv is that the linker be longer than 12 amino acids.*" (col. 12, l. 10-11).

Coloma and Morrison teach a bispecific antibody in which the hinge of a first scF_v of one specificity is fused to the **constant region** of a second antibody with a different specificity. The constructs of Coloma and Morrison comprises a single-chain having four variable domains and a constant region. For joining the hinge of one scF_v with the constant region of the other scF_v Coloma and Morrison use a five amino acid linker. However, Coloma and Morrison do not teach or suggest to use a five amino acid linker for connecting variable domains. For joining the V_H and V_L domains Coloma and Morrison use the 15 residue linker $(Gly_4\text{-}Ser)_3$ (see page 162 "Experimental protocol"). Thus, consistent with the teaching of Mezes et al., Coloma and Morrison discloses that for a scF_v the linker joining the V_H and V_L domains has to be long enough to allow the pairing of the adjacent domains.

In view of the distinct structural and functional differences between the claimed invention and the antibodies disclosed in the cited references and the failure of Hollinger et al. to motivate a skilled artisan to modify Mezes et al. to arrive at the present invention, Applicants submit that a prima facie case of obviousness has not been established under 35 USC §103(a). Withdrawal of this ground of rejection is therefore respectfully requested.

CONCLUSION

Applicant submits that this paper fully addresses the Office Action mailed September 21, 2005. Should the Examiner have any questions, the Examiner is encouraged to contact the undersigned attorney at (650) 565-3585. The Commissioner is hereby authorized to charge any required fees due in connection with this submission, including petition and extension of time fees, and to credit any overpayment, to Deposit Account No. 23-2415 (Docket No. 31304-756.831).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

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By: _____
Albert Halluin, Reg. No. 25,227

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Tel: (650) 565-3585
Fax: (650) 493-6811
Customer No. 21971